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Prefrontal cortical thinning links to negative symptoms in schizophrenia via the ENIGMA consortium

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Abstract

Background

Our understanding of the complex relationship between schizophrenia symptomatology and etiological factors can be improved by studying brain-based correlates of schizophrenia. Research showed that impairments in value processing and executive functioning, which have been associated with prefrontal brain areas (particularly the medial orbitofrontal cortex (MOFC)), are linked to negative symptoms. Here we tested the hypothesis that MOFC thickness is associated with negative symptom severity.

Methods

This study included 1 985 individuals with schizophrenia from seventeen research groups around the world contributing to the ENIGMA Schizophrenia Working Group. Cortical thickness values were obtained from T1-weighted structural brain scans using FreeSurfer. A meta-analysis across sites was conducted over effect sizes from a model predicting cortical thickness by negative symptom score (harmonized SANS or PANSS scores).

Results

Meta-analytical results showed that left, but not right, MOFC thickness was significantly associated with negative symptom severity (β_{std}=-0.075; *p*=0.019) after accounting for age, gender and site. This effect remained significant (p=0.036) in a model including overall illness severity. Covarying for duration of illness, age of onset, antipsychotic medication or

handedness weakened the association of negative symptoms with left MOFC thickness. As part of a secondary analysis including ten other prefrontal regions further associations in the left lateral orbitofrontal gyrus and pars opercularis emerged.

Conclusions

Using an unusually large cohort and a meta-analytical approach, our findings point towards a link between prefrontal thinning and negative symptom severity in schizophrenia. This finding provides further insight into the relationship between structural brain abnormalities and negative symptoms in schizophrenia.

Introduction

Although advances have been made in our understanding of the pathophysiology of schizophrenia, the heterogeneity of the disorder impedes the effectiveness of biological and clinical research. The large number of cognitive and clinical symptoms within the syndrome and their considerable variability across patients likely reflects the impact of various etiological factors (Jablensky, 2006). Such variability makes it harder to achieve a comprehensive understanding underlying brain pathology. Investigations using large sample sizes to study symptoms associated with dimensions of behavior that can be measured quantitatively, may advance our understanding of brain behavior relationships within as well as across diagnostic categories. Investigating distinct symptoms of the disorder as a continuous variable may reveal more specific neurobiological mechanisms in schizophrenia.

Negative symptoms are characterized by flat or blunted affect, inability to experience pleasure (anhedonia), poverty of speech, lack of motivation and interest (avolition/apathy) and lack of desire to form relationships (Andreasen & Olsen, 1982). Patients with predominantly negative symptoms have poor pre-morbid adjustment during childhood or early adolescence and a low employment rate during adulthood, achieve low educational attainment and exhibit considerable cognitive impairment (Milev *et al.* 2005; Rosenheck *et al.* 2006; Jeppesen *et al.* 2008).

Studies have shown widespread cortical thickness reductions across the brain in patients with schizophrenia compared to healthy controls with frontal and temporal regions

being generally more affected than others areas (Nesvåg *et al.* 2008; Goldman, 2009; Schultz *et al.* 2010). In line with prior work, Ehrlich *et al*. (2012) and Geisler *et al.* (2015) recently reported marked reductions of cortical thickness in patients with schizophrenia, which were also related to executive functioning.

Executive functioning is often driven by incentives and motivation (Pessoa, 2009). When we make decisions between options with different (subjective) value or learn from positive or negative feedback, those processes are governed by a neural circuit that centers around structures such as the ventral striatum and the medial orbitofrontal cortex (MOFC) (Schlagenhauf *et al.* 2014; Deserno *et al.* 2016). Within this circuit, the MOFC is predominately linked to (subjective) value processing and positive affect (Burgdorf & Panksepp, 2006; Peters & Büchel, 2010; Grabenhorst & Rolls, 2011; Liu *et al.* 2011; Price & Harmon-Jones, 2011; Berridge & Kringelbach, 2015), which is impaired in schizophrenia (Cohen & Minor, 2010; Kalkstein *et al.* 2010). MOFC lesions in humans relate to deficits in reward-based learning, which can result in apathy and lack of affect (Hornak *et al.* 2003; Fellows & Farah, 2005; Fisher *et al.* 2011; Kühn & Gallinat, 2012). Accordingly, functional and structural imaging studies in healthy cohorts have reported associations between MOFC activity (and thickness) and characteristics that are comparable to the negative symptoms observed in schizophrenia (Harvey *et al.* 2007; Ducharme *et al.* 2014). For instance, functional connectivity between the orbitofrontal cortex and the dorsolateral prefrontal cortex was found to be dependent on levels of motivation (Szatkowska *et al.* 2008).

Given these findings one could hypothesize that altered brain structure and functioning in the orbitofrontal cortex may represent one of the potential mechanisms underlying negative symptoms in schizophrenia. This is motivated by the idea that i) neural representations of decision values may not be adequately generated and ii) reward feedback might not get completely transformed into motivational drive for goal-directed behaviour (Barch & Dowd, 2010; Deserno *et al.* 2013).

Several functional imaging studies have assessed the brain-based correlates of negative symptoms in schizophrenia. An early PET study found lower perfusion of several brain regions – including the MOFC – during hedonic judgments of positive and negative visual stimuli in patients with schizophrenia (Plailly *et al.* 2006). More recent fMRI studies in patients with schizophrenia found neural responses in the medial prefrontal cortex to be exaggerated upon omission of expected reward but blunted upon receipt of unexpected reward (Schlagenhauf *et al.* 2009). Simon *et al*. (2015) showed that neural responses in the ventral striatum during a reward anticipation paradigm were negatively associated with apathy – a core negative symptom; while no associations between ventral striatal responses and positive symptoms were observed. Importantly, they found lower connectivity between the ventral striatum and the MOFC in individuals with schizophrenia compared with controls. Furthermore, in one of the aforementioned studies focussing on receipt of unexpected reward in schizophrenia, medial frontal cortical activation predicted task-related motivation, which in turn predicted anhedonia severity (Segarra *et al.* 2016). In line

with this, another study could show that activity in the orbitofrontal cortex during hedonic processing was negatively correlated with anhedonia severity in people with schizophrenia (Harvey *et al.* 2010).

With respect to structural imaging, gray matter density of the orbitofrontal cortex has also been associated with self-fulfillment achievement motivation in healthy individuals (Takeuchi *et al.* 2014). In patients with schizophrenia, Venkatasubramanian *et al*. (2008) found that lower left MOFC thickness was associated with higher negative symptom severity. Similar findings have been reported by Nenadic *et al*. (2015), providing further evidence for the involvement of medial prefrontal regions in negative symptoms; though some negative findings also exist (Crespo-Facorro *et al.* 2011; Xiao *et al.* 2013).

Reasons for these inconsistencies may be two-fold. First, most studies conducted to date have had rather moderate sample sizes, investigating on average about a hundred patients. Second, moderating effects of confounders such as antipsychotic medication, illness severity, or duration of illness that may influence the association between thickness and negative symptoms have not been investigated extensively. Analyses of larger samples will increase power allowing to understand prior inconsistencies in findings as well as to study potential moderator effects.

Here we set out to investigate the structural correlates of negative symptoms in a large meta-analysis including almost 2 000 individuals with schizophrenia. Based on previous structural imaging findings, we hypothesised that lower MOFC thickness is associated with

negative symptom severity in schizophrenia. As part of an exploratory analysis we also aimed to understand relationships with cortical thickness in other prefrontal brain regions.

Methods

Study samples

The current study includes a total of 1 985 individuals with schizophrenia or schizophrenia spectrum diagnoses (see also SM section 2.1, subsection s) from seventeen research groups around the world as part of the ENIGMA Schizophrenia Working Group as described previously (van Erp *et al.* 2015). Schizophrenia diagnosis was based on the Diagnostic and Statistical Manual of Mental Disorders (DSM, editions III-R or IV) or the International Classification of Diseases (ICD, edition 10) criteria using either the Structured Clinical Interview for DSM Disorders (SCID), the Comprehensive Assessment of Symptoms and History (CASH), the Present State Examination (PSE), and/or a review of case files/medical records by trained clinicians. All individuals had negative symptom ratings and structural imaging data available. Mean sample size at each research site was 117 patients (range: 23-244). See supplementary Table 1s for more details.

Each study sample was collected with participants' written informed consent approved by local Institutional Review Boards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and

institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. No individual subject imaging or clinical data were shared among the ENIGMA institutions.

Negative symptom measures and score conversion

Negative symptom severity was assessed using the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) and the Positive and Negative Syndrome Scale (PANSS) (Kay *et al.* 1987). Negative symptom scores were calculated as follows:

1. Total SANS (Composite) score = sum of SANS items 1-7, 9-12, 14-16, 18-21, and 23-24;
2. Global SANS (Summary) score = sum of SANS items 8, 13, 17, 22, and 25 (which include affective flattening, alogia, avolition, anhedonia, and attention global rating scores, respectively); or
3. PANSS Negative = sum of PANSS items 8-14.

To harmonize scores, we decided to convert all negative scores (i.e. PANSS Negative and Total SANS Composite scores) to Global SANS (Summary) scores following recommendations by Andreasen (1983) and using the algorithms published in van Erp *et al*. (2014). For additional details see supplementary Section 1.1.

Image acquisition and processing

Based on the previous literature (Venkatasubramanian *et al.* 2008; Nenadic *et al.* 2015) we followed a region-of-interest (ROI) approach, focusing on the medial orbitofrontal cortex (MOFC), while ten other prefrontal regions were considered in additional exploratory analyses (see SM section 2.2). Left and right MOFC thickness values – based on the Desikan-Killiany atlas (Desikan *et al.* 2006) - were obtained using FreeSurfer (http://surfer.nmr.mgh.harvard.edu) from high-resolution T1-weighted structural brain scans. Details on study type (single site or multisite), scanner vendor/strength/sequence, acquisition parameters and FreeSurfer versions used are provided in supplementary Table 1s. For quality control, histograms of MOFC thickness values were generated and outliers were visually inspected by overlaying their parcellation on the subjects' anatomical images. Only parcellations judged to be accurate upon visual inspection were subjected to statistical analyses (see supplementary Table 1s for information on outlier removal and Figure 1s for left and right MOFC thickness descriptives by sample).

Statistical analyses

Within each sample, an association of negative symptoms with left and right MOFC thickness was analyzed using univariate linear regression analysis (R's linear model function *lm*) predicting mean MOFC thickness by global SANS score. The main analysis included age

and gender as covariates. In cases of multi-site studies (FBIRN, MCIC, UMCU and Osaka) binary dummy covariates were included in the model to account for n−1 sites. For samples where information was available, secondary models were run separately with each of the following covariates: 1) current antipsychotic medication (by medication group: atypical/typical/both/none; and by using chlorpromazine (CPZ) equivalents as described in Woods *et al.* (2003), available in a subsample of n = 1 178), 2) duration of illness, 3) age of onset (defined as onset of symptoms), 4) illness severity (measured using PANSS Total score), and 5) handedness (right/left/ambidextrous). Additional exploratory analyses were carried out to investigate the link between negative symptom severity and cortical thickness in schizophrenia spectrum subtypes and in ten additional frontal brain regions. Results were ranked according to effect size. In addition, Bonferroni correction was applied to account for multiple testing (see SM section 2.2 for more details). Analyses of individual subject data were performed by the site that contributed the sample, using code created within the ENIGMA collaboration.

Meta-analyses

From each sample, standardized regression coefficients were extracted from the main and secondary models as a measure of effect size for the left and right MOFC using the *lm.beta* function in the lm.beta R package (Behrendt, 2014). A meta-analysis was conducted over these effect sizes using the *rma* function in the R package metaphor (Viechtbauer,

2010). We meta-analyzed the estimates across sites by weighting Fisher's r-to-z transformed effect size values by sample size in a random-effects model using the default REML estimator. The same procedure was used to investigate the effects of age, gender, illness severity and duration of illness on MOFC thickness. For analyses, in which both left and right MOFC were analyzed, the significance threshold was corrected for two tests (p=0.05/2=0.025). Descriptives are weighted by the sample size at each site using the weighted.mean procedure in R (R Development Core Team 2008).

Due to between-site differences in study characteristics such as antipsychotic medication, handedness and single vs multisite status (supplementary Table 1s), we used moderator analyses to investigate between-sample differences.

Results

Demographics

Mean age (weighted by sample-size) across patient samples was 34 years (range: 28-43). Mean patient samples were 68% male (range: 55-76%). The weighted mean duration of illness across the patient groups was 10 years (range: 1-20) and mean age of onset was 24 years (range: 19-29). For samples where current antipsychotic type and dose information was available, the weighted percentage of patients on first-generation (typical), second-generation antipsychotics (atypical), both typical and atypical or no antipsychotic

medication was 11%, 71%, 9% and 9%. Ninety percent of patients were right-handed (range: 68-95), while only 8% (range: 2-14) were left-handed and 2% (range: 0-25) were ambidextrous (Table 1 and supplementary Table 1s).

Meta-analysis

The weighted mean global SANS scores across the samples was 7.91 (range: 2.86-12.90). Weighted mean MOFC thickness was 2.46 mm (range: 2.26-2.71) in the left hemisphere and 2.42 mm (range: 2.17-2.61) in the right hemisphere. Meta-analytical results showed that global SANS scores were negatively associated with left MOFC thickness (β_{std}=-0.075; p_{SANS}=0.019; Figure 1) after accounting for age, gender and number of sites (if applicable). Funnel plot inspection gave no indication of bias (Egger's p=0.193; supplementary Figure 2s). However, effect sizes were found to be heterogeneous (Q(16)=26.399; p=0.049; I^2=42.38%). We found only a trend effect (but in the same direction) of global SANS on right MOFC thickness (β_{std}=-0.064; p_{SANS}=0.055). For detailed results, see supplementary Section 2.1, sections a and b).

Effects of covariates and moderator analyses

We carried on investigating both within-sample and moderating between-sample effects of age, gender, illness severity, duration of illness and age of onset as well as

antipsychotic medication, handedness, schizophrenia spectrum subtypes and multisite status based on samples, for which this information was available (supplementary Table 1s).

While a meta-analysis of within-sample effects indicated that left MOFC thickness decreased with age (β_{std}=-0.237; p<0.0001) and was lower in women (β_{std}=-0.090; p<0.0001), the main association of global SANS and left MOFC thickness remained significant (β_{std}=-0.075; p_{SANS}=0.019, see main model above and supplementary section 2.1, subsections a, c and d).

Overall illness severity (although correlated with negative symptoms; R^2 = 59.5%) did not associate with left MOFC thickness (p=0.555) after accounting for age, gender and site (if applicable), while the global SANS effect in the same model remained significant (β_{std}=-0.113; p_{SANS}=0.036; see also supplementary section 2.1, subsections e and f).

Duration of illness correlated negatively with left MOFC thickness (Fisher's z=-0.145; p<0.001), but not with global SANS score (p=0.190). While duration of illness also correlated strongly with age (Fisher's z=0.834; p<0.001), it did not associate with left MOFC thickness above and beyond age in the lower regression models (p=0.199). However, additionally accounting for duration of illness within each sample also reduced the main effect of SANS on left MOFC thickness (p_{SANS}=0.068; see supplementary section 2.1, subsections g and h). Similar diminishing effects were observed when investigating the influence of age of onset (which was highly correlated with duration of illness; Fisher's z=-0.658; p=0.015), antipsychotic medication and handedness within each sample, which themselves did not

moderate the global SANS – left MOFC thickness relationship between samples (p_{AO}=0.737; p_{med}=0.447; p_{hand}=0.580; see supplementary section 2.1, section i, j and k). Investigating the effects of antipsychotic medication further, we found that mean left MOFC thickness estimates (p=0.007), but not mean global SANS estimates (p=0.454) differed by antipsychotic medication type (i.e. percentages of patients in each medication group in each sample, supplementary section 2.1, subsections l and m). Specifically, compared to unmedicated patients, left MOFC reductions were larger at sites with a larger percentage of patients treated with atypical (β_{std}=-0.006; p=0.002) or typical AP (β_{std}=-0.007; p=0.003). Proportion of patients, who were treated with both antipsychotic medication types, was not associated with MOFC thickness (p=0.444; supplementary section 2.1, subsection l). The reductions observed in patients treated with atypical (but not typical) antipsychotic medication remained significant in analyses that included gender, age, or duration of illness as covariates (supplementary section 2.1, subsection n and o). Current medication in CPZ units was not linked to left MOFC thickness (p_{CPZ}=0.170), while the main effect of negative symptom severity remained significant (β_{std}=-0.095; p_{SANS}=0.040; supplementary section 2.1, subsection q and r). Our main findings also remained stable (β_{std}=-0.078; p_{SANS}=0.022), when restricting the analyses to patients with DSM-IV schizophrenia subtypes or schizoaffective / -phreniform disorder only (supplementary section 2.1, subsection s).

Effect on other frontal regions

Exploratory analyses were used to analyse the associations between negative symptoms and ten other frontal brain regions (separately for the left and right hemisphere), controlling for sex, age and site (if applicable). Regions with effects similar in size to the left MOFC were found in the left pars opercularis (β_{std}=-0.082), the left and right lateral orbitofrontal gyrus (left: β_{std}=-0.076, right: β_{std}=-0.073), and the left superiorfrontal gyrus (β_{std}=-0.066). After Bonferroni correction for multiple testing, two regions – the left lateral orbitofrontal gyrus (corrected p_{SANS}=0.034) and left the pars opercularis (corrected p_{SANS}=0.02) - remained significant (SM section 2.2). The direction, size and lateralization of the effect compared well to our main results.

Discussion

Summary

In this study, we investigated the relationship between MOFC thinning and negative symptom severity in schizophrenia. We found that negative symptoms related inversely to cortical thickness in this brain region, with effects appearing greater in the left hemisphere compared to the right. This finding was independent of general illness severity, age and gender, but somewhat lessened when covarying for the influence of antipsychotic medication, age of onset and duration of illness (with the latter two variables being highly correlated). Exploratory analyses identified associations between negative symptoms and

thickness in the lateral orbitofrontal gyrus and pars opercularis in the left hemisphere. Our investigation has a number of strengths. First, using a meta-analytical approach, we were able to increase our sample size by a magnitude of 10 compared to previous studies. Second, the large sample allowed for the investigation of potentially influencing, but small effects of age, gender, illness severity, duration of illness, age of onset, antipsychotic medication, and handedness. Third, our sample included diverse patient groups that spans a broad age range allowing for a generalization of our findings.

Cortical thickness in the left medial orbitofrontal cortex and negative symptoms

Our results are in agreement with two previously published studies. Specifically, the association between MOFC thickness and negative symptoms in the study by Venkatasubramanian *et al*. (2008) was also negative and only present in the left hemisphere. Comparing patient groups with distinct symptom profiles, the study by Nenadic *et al*. (2015) also reported prefrontal reductions (including the MOFC) in patients characterized by predominantly negative symptoms compared to subgroups with predominantly paranoid and disorganised symptoms. However, there have also been reports, which failed to identify an association between MOFC thickness and negative symptoms (Xiao *et al.* 2013; Bodnar *et al.* 2014; Ansell *et al.* 2015; McKechanie *et al.* 2015). There are several potential explanations for these discrepant findings. First, all previous studies were based on rather small samples (between 40 and 130 patients) and hence

potentially underpowered to detect the weak, but robust association, we were able to identify in our study based on almost 2 000 patients. Furthermore, previous samples differed substantially in important characteristics such as illness chronicity and mean age. Of note, all studies that accepted the null hypothesis consisted of young (< 25 years), first-episode patients, while studies which reported effects, such as by Venkatasubramanian *et al*. (2008) and Nenadic *et al*. (2015), included older (>30 years), chronic patients. Similarly, mean age across our samples ranged from 28 – 43 years while mean duration of illness was 10 years, indicating that the association between negative symptoms and MOFC thickness might be more apparent when patients are older or in later stages of the disorder.

Animal and human studies suggest that neurons in the MOFC encode the subjective value of expected reward (Furuyashiki & Gallagher, 2007; Roesch & Olson, 2007), providing evidence that the MOFC mediates processes associated with the learning and retrieval of (subjective) value information, which guides decision-making and goal-directed behaviour (Bechara *et al.* 1994, 2000). Several studies suggest that negative symptoms in schizophrenia are associated with reinforcement learning abnormality (Waltz *et al.* 2007; Strauss *et al.* 2011). Gold *et al*. (2012) observed that patients with high-negative symptoms were less able to take expected reward values into account during decision making processes. As a result, patients fail to learn actions that lead to positive outcomes, while they outperform controls in avoiding punishing outcomes, showing that the findings were not indicative of general learning deficits, but of deficits in reward-related learning. Such

findings may help to explain the high prevalence of avolition and anhedonia in schizophrenia, two core dimensions of negative symptomatology. In line with this, aberrant neural responses to reward feedback was observed in medial prefrontal areas of patients with schizophrenia (Schlagenhauf *et al.* 2009), although results from this and several other studies also emphasize the relevance of ventral striatal pathways pointing towards an involvement of a wider striatal-prefrontal network in reward feedback (Schlagenhauf *et al.* 2014; Mørch-Johnsen *et al.* 2015; Radua *et al.* 2015).

The involvement of additional frontal brain regions is also supported by the results of our study, as exploratory analyses showed further associations of negative symptoms with the left lateral orbitofrontal gyrus and left pars opercularis. In line with our initial hypothesis, the lateral orbitofrontal gyrus is also predominantly involved in value processing (Kringelbach & Rolls, 2004; Zald *et al.* 2014). The pars opercularis is mainly linked to language processing (Belyk & Brown, 2014), which might relate to poverty of speech. An association of comparable effect size to our main finding, but not significant after Bonferroni correction, was also identified in the superior frontal gyrus (including the pre-supplementary motor area that is involved in volition (Haggard 2008; Bracht *et al.* 2013)), which might be associated with the lack of ability for spontaneous, self-generated action that relates strongly to the avolition subdomain of negative symptoms.

We observed a significant association between grey matter thickness and negative symptoms only in the left hemisphere. This aligns well with several other reports of

significant grey matter reductions in frontal regions of the left hemisphere (but not the right hemisphere) in patients with schizophrenia (Suzuki *et al.* 2002; Kawasaki *et al.* 2004; Honea *et al.* 2005; Kawasaki *et al.* 2008;). Moreover, cerebral lateralization of patients with schizophrenia tends to be less leftward lateralized and may even be rightward lateralized rather than symmetric. While some have argued that this might possibly reflect perturbations in the lateralization process underlying left cerebral dominance for language (Kawasaki *et al.* 2008), others believe that this atypical lateralization represents a greater involvement of the right hemisphere, which may relate to a broader, more diffuse semantic network (Grabner *et al.* 2007). With respect to value processing, the left prefrontal cortex has been linked stronger to motivation and positive affect than the right (Davidson, 2004; Price & Harmon-Jones, 2011). Hence, structural abnormalities in this region could link to deficits in the capacity to experience positive affect, a hallmark feature of negative symptoms.

In sum, our finding of a negative association between left MOFC thickness and negative symptoms underline the importance of this region in motivational and executive functioning, which is commonly impaired in schizophrenia patients (Barch & Dowd, 2010).

Potential moderators

Illness severity

We found that the effect of negative symptoms on left MOFC thickness was independent of general illness severity. That is, the MOFC might be specifically involved in motivational and executive aspects of schizophrenia as opposed to general schizophrenia psychopathology. Two other cortical thickness studies also failed to identify a significant correlation between illness severity (as measured using PANSS total scores) and thickness in any cortical region (Rimol *et al.* 2010; Oertel-Knöchel *et al.* 2013). Furthermore, van Haren *et al*. (2011) identified an association between *poor functional and symptomatic outcome* (derived using a factor analysis on Global Assessment of Functioning (GAF), the Camberwell Assessment of Need scale, and PANSS) and cortical thinning in the superior temporal gyrus, but not in frontal areas. Also in line with this is a functional imaging study by Simon *et al*. (2015), who investigated whole-brain activation during a reward anticipation paradigm. The authors observed that negative symptoms (especially signs of apathy), but not positive symptoms, were inversely correlated with activation in the ventral striatum, which at the same time showed reduced connectivity with the MOFC in patients compared to controls, further supporting the role of the MOFC in negative symptoms in schizophrenia.

Duration of illness

Duration of illness correlated strongly and negatively with left MOFC thickness (but not with negative symptom scores), although effects were dependent on age effects on thickness. Negative symptoms no longer predicted thickness significantly when covarying

for age *and* duration of illness (which was highly correlated with age and not predictive of MOFC thickness in the combined model) in the same model. This may indicate that some of the variance in thickness explained by negative symptoms depends on these variables. In this respect and as explained above, it is of interest that studies of first-episode patients did not find an association between symptoms and thickness in the MOFC. Ansell *et al*. (2015) studied very young (mean age of 22 years) psychosis patients, who had been diagnosed for the first time within the last three months. The authors found no effects of negative symptoms on thickness in prefrontal areas (although they did report that negative symptoms related to reduced thickness in parietal regions, but only in patients treated with first-generation antipsychotics). Crespo-Facorro *et al*. (2011) also studied first-episode patients and reported no significant relationship between negative symptoms and lobar cortical thickness. In the light of these previous findings and considering that participants in our study were predominantly older, chronic patients, our results might be more specific to later stages of the disorder.

Antipsychotic medication

Although the relationship between negative symptoms and left MOFC thickness did not vary by antipsychotic medication group in our moderator analysis, some amount of variance in left MOFC thickness was explained through antipsychotic medication effects, with patients treated with atypical antipsychotics showing the most robust reductions.

Notably, when we used current medication in CPZ equivalent units as a quantitative measures of antipsychotic medication (at the cost of a reduced sample size), an effect on MOFC thickness was not observed. While past studies predominantly reported volume and thickness deficits in frontal brain regions in patients treated with typical compared to those treated with atypical antipsychotics or unmedicated patients (van Haren *et al.* 2011; Lesh *et al.* 2015; Vita *et al.* 2015), there have also been many conflicting findings (Cahn *et al.* 2002; Ho *et al.* 2011). Attempting to reconcile previous reports, it has been suggested that antipsychotic medication effects on brain structure might be substance-specific (Xiao *et al.* 2008) and might also depend on illness chronicity and the duration of untreated psychosis. Some studies reported that medication effects on frontal brain structures were apparent especially during the early phase of treatment and that the effect size increased with longer durations of untreated psychosis (for a review see (Aderhold *et al.* 2014)). Genetic predisposition and substance use could also interact with antipsychotic medication (Tregellas *et al.* 2007; Hartz *et al.* 2010). With respect to our own findings we would like to stress that this is a purely correlational result, which does not in any way imply a causal relationship between antipsychotic medication intake and cortical thinning. Considering that we only investigated the possible effect of current antipsychotic medication, future studies are necessary to investigate this relationship in more detail by studying estimates of cumulative antipsychotic medication such as equivalent dose by time of exposure or treatment intensity in dose-years (Andreasen *et al.* 2010, 2013).

Limitations

The results of this study have to be seen in the light of the following limitations. First, our study was strongly hypothesis-driven in that we focussed on effects in the medial orbitofrontal cortex due to its role in value processing. As part of our exploratory analyses we also identified associations of comparable effect size in other brain regions including the pars opercularis and lateral orbitofrontal gyrus. Further studies are needed to investigate whether these associations are driven by processes that are not directly linked to value processing. Secondly, given the cross-sectional design of this study, we were unable to address directional effects. That is, we were not able to determine whether cortical thinning precedes or follows the development of negative symptoms. A range of factors such as measures of cumulative antipsychotic medication or relapse duration (Andreasen *et al.* 2010, 2013), which we were unable to investigate, might modulate the observed association and should be investigated in subsequent studies. Third, we included patients within the schizophrenia spectrum and used a measure of global negative symptom severity, but it is possible that effects were driven by schizophrenia subtype or subdimension-specific characteristics.

Conclusion

We investigated the relationship between negative symptoms and cortical thickness in the medial orbitofrontal cortex in a large cohort of schizophrenia patients, comprising almost 2 000 patients. Negative symptom severity was significantly associated with thickness in this region in the left, but not the right hemisphere. This association was irrespective of age, gender and illness severity, but possibly modulated by antipsychotic medication and duration of illness. Our findings provide further insight into symptom-related pathophysiological processes of schizophrenia.

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Conflict of interest

The authors of this manuscript have no financial conflicts of interest to disclose.

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Table

	estimate	range	data available for N number of studies
% males	68	55-76	17
Mean age in years	34	28-43	17
Mean SANS Global	7.91	2.86-12.90	17
Mean duration of illness in years	10	1-20	13
Mean Age of Onset in years	24	19-29	13
Mean illness severity (PANSS Total)	70.43	49.81-90.22	9
Antipsychotic medication			13
%Atypical (N)	71 (1201)	39-91	
%Typical (N)	11 (202)	0-45	
%Both A & T (N)	9 (157)	0-24	
%None (N)	9 (149)	0-53	
Mean Chlorpromazine equivalents	423.32	97.48-637.80	12
Handedness			14
%Right	90	68-95	
%Left	8	2-14	
%Ambidextrous	2	0-25	
Cortical thickness in mm			17
Mean left medial orbitofrontal	2.46	2.26-2.71	
Mean right medial orbitofrontal	2.42	2.17-2.61	

Table 1. Demographics. Means are weighted by study sample size.

Figure legend

Figure 1. Forest plot of association between global SANS and cortical thickness in the left medial orbitofrontal cortex across all 17 study sites, controlling for age, gender and number of sites (if applicable; of note the global SANS-left MOFC thickness relationship did not differ between single vs multisite samples (p=0.422; see supplementary section 2.1, subsection o)). Fisher's transformed standardized regression coefficients are denoted by black boxes. Black lines indicate 95% confidence intervals. The combined estimate for all sites is represented by a black diamond with the outer edges of the diamond indicating the confidence interval limits.

Supplementary Materials

SM 1 Method

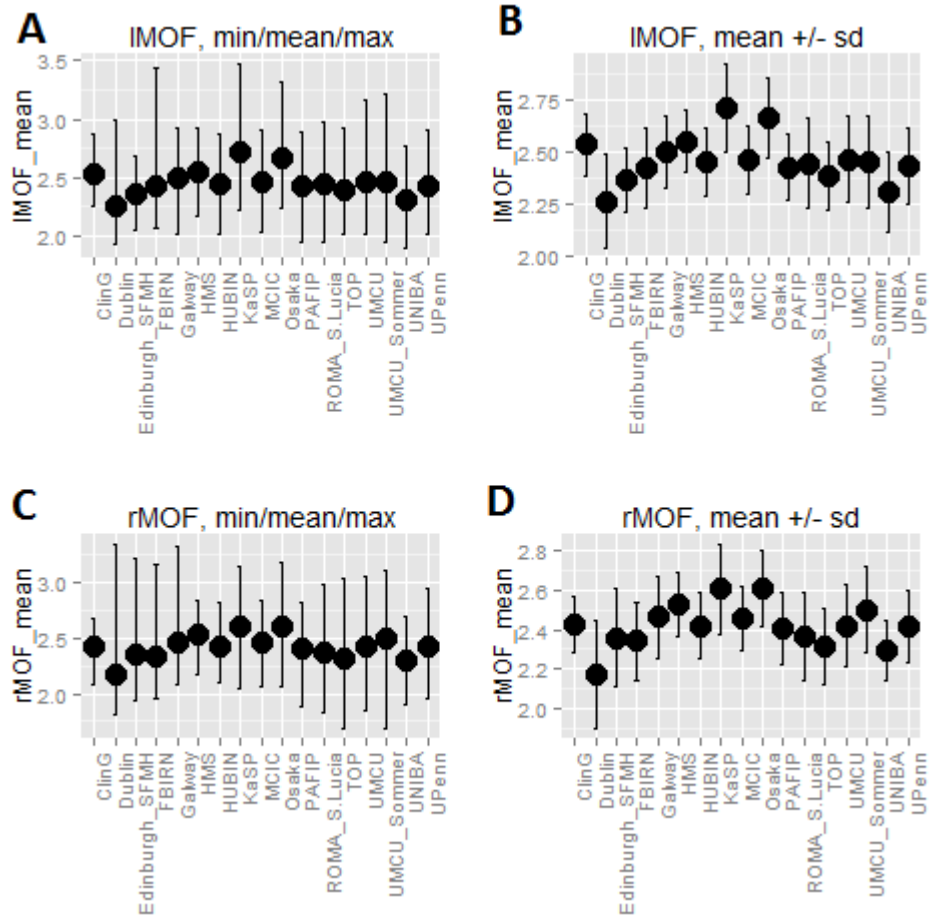
SM 1.1 Symptom score conversion algorithms

Global SANS (Summary) Score = -2.0671 + (0.665*PANSS Negative score)

Global SANS (Summary) Score = 1.0863 + (0.2943*Total SANS (composite) score)

SM 1.2 Imaging descriptives and quality control

Parcellations were visually inspected and statistically evaluated for outliers following standardized ENIGMA protocols (http://enigma.ini.usc.edu/protocols/imaging-protocols). Each image parcellation was individually examined by a neuroimaging expert at each site by overlaying the parcellation label of each structure on the T1-weighted brain scan. Further, we collected study-wide statistics (means, minimums, maximums, and standard deviations; see SM Figure 1s) as well as histogram and diagnostic plots in order to identify non-normally distributed data and major outliers. A subject was considered a statistical outlier if its thickness was >2.698 standard deviations away from the global mean. For each subject that was marked as a statistical outlier, individual sites were asked to re-inspect the subject's parcellations in order to verify that it was properly segmented. If a subject was a statistical outlier, but was properly segmented it was kept in the analysis. Otherwise the subject was removed (see SM Table 2s for details).



SM Figure 1s. Left (A-B) and right (C-D) medial orbitofrontal cortical thickness descriptives (min/mean/sd/max) by study site.

SM 2 Results

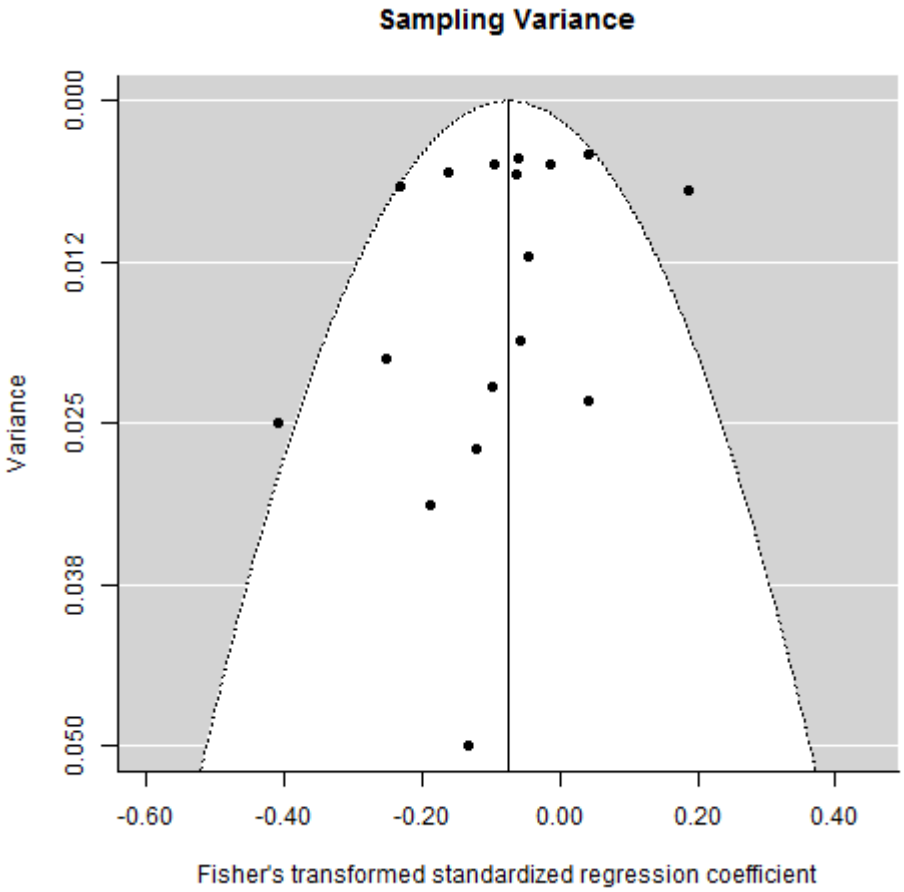
SM 2.1 Detailed results of meta-analyses

a) Main model: left MOFC <- global SANS + gender + age + site (if applicable)

In the main model we investigated the effect of global SANS scores on left MOFC thickness, covarying for gender, age and the number of sites as dummy variables (where applicable). Shown below are the estimate, the standard error, p value and the confidence intervals for the meta-analytical standardized regression beta of the global SANS score on left MOFC thickness. Results were based on estimates from 17 studies using a restricted maximum likelihood (REML) approach. Also provided are estimates and significance levels for effect size heterogeneity between studies.

```
Random-Effects Model (k = 17; tau^2 estimator: REML)

tau^2 (estimated amount of total heterogeneity): 0.0067 (SE =
0.0057)
tau (square root of estimated tau^2 value):      0.0816
I^2 (total heterogeneity / total variability):   42.38%
H^2 (total variability / sampling variability):  1.74

Test for Heterogeneity:
Q(df = 16) = 26.3994, p-val = 0.0487

Model Results:

estimate       se     zval     pval    ci.lb    ci.ub
 -0.0752   0.0321  -2.3446   0.0190  -0.1381  -0.0123        *
```

Funnel plot main model



SM Figure 2s. Funnel plot. Individual study regression coefficients are plotted against sample variance (a measure of the precision of the data).

b) Exploratory model: right MOFC <- global SANS + gender + age + site (if applicable)

Shown below are the estimate, the standard error, p value and the confidence intervals for the meta-analytical standardized regression beta of the global SANS score on right MOFC thickness. Results were based on estimates from 17 studies.

```
Random-Effects Model (k = 17; tau^2 estimator: REML)


tau^2 (estimated amount of total heterogeneity): 0.0080 (SE =
0.0063)

tau (square root of estimated tau^2 value):      0.0892

I^2 (total heterogeneity / total variability):   46.78%

H^2 (total variability / sampling variability):  1.88


Test for Heterogeneity:

Q(df = 16) = 28.4025, p-val = 0.0283


Model Results:


estimate       se     zval     pval    ci.lb    ci.ub

 -0.0643   0.0335  -1.9207   0.0548  -0.1299   0.0013        .
```

c) Effects of covariates: left MOFC <- global SANS + gender + age + site (if applicable)

Shown below are the estimate, the standard error, p value and the confidence intervals for the meta-analytical standardized regression beta of age on left MOFC thickness. Results were based on estimates from 17 studies.

```
Random-Effects Model (k = 17; tau^2 estimator: REML)


tau^2 (estimated amount of total heterogeneity): 0.0117 (SE =
0.0078)

tau (square root of estimated tau^2 value):      0.1083

I^2 (total heterogeneity / total variability):   56.43%

H^2 (total variability / sampling variability):  2.30
```

```
Test for Heterogeneity:
Q(df = 16) = 36.1039, p-val = 0.0028

Model Results:

estimate       se     zval     pval    ci.lb    ci.ub
 -0.2372   0.0371  -6.3925   <.0001  -0.3100  -0.1645      ***
```

d) Effects of covariates: left MOFC <- global SANS + gender + age + site (if applicable)

Shown below are the estimate, the standard error, p value and the confidence intervals for the meta-analytical standardized regression beta of gender on left MOFC thickness. Results were based on estimates from 17 studies.

```
Random-Effects Model (k = 17; tau^2 estimator: REML)

tau^2 (estimated amount of total heterogeneity): 0 (SE =
0.0026)
tau (square root of estimated tau^2 value):      0
I^2 (total heterogeneity / total variability):   0.00%
H^2 (total variability / sampling variability):  1.00

Test for Heterogeneity:
Q(df = 16) = 13.5923, p-val = 0.6291

Model Results:

estimate       se     zval     pval    ci.lb    ci.ub
 -0.0900   0.0227  -3.9592   <.0001  -0.1346  -0.0455      ***
```

e) Effects of covariates: left MOFC <- global SANS + illness severity + gender + age + site (if applicable)

Shown below are the estimate, the standard error, p value and the confidence intervals for the meta-analytical standardized regression beta of illness severity on left MOFC thickness. Results were based on estimates from 9 studies.

```
Random-Effects Model (k = 9; tau^2 estimator: REML)

tau^2 (estimated amount of total heterogeneity): 0.0387 (SE =
0.0254)
tau (square root of estimated tau^2 value):      0.1967
I^2 (total heterogeneity / total variability):   81.26%
H^2 (total variability / sampling variability):  5.34

Test for Heterogeneity:
Q(df = 8) = 44.9511, p-val < .0001

Model Results:

estimate       se     zval     pval    ci.lb    ci.ub
  0.0446   0.0755   0.5908   0.5546  -0.1034   0.1927
```

f) Effects of covariates: left MOFC <- global SANS + illness severity + gender + age + site (if applicable)

Shown below are the estimate, the standard error, p value and the confidence intervals for the meta-analytical standardized regression beta of global SANS score on left MOFC thickness. Results were based on estimates from 9 studies.

```
Random-Effects Model (k = 9; tau^2 estimator: REML)


tau^2 (estimated amount of total heterogeneity): 0.0145 (SE =
0.0126)

tau (square root of estimated tau^2 value):      0.1205

I^2 (total heterogeneity / total variability):   61.91%

H^2 (total variability / sampling variability):  2.63


Test for Heterogeneity:

Q(df = 8) = 21.8200, p-val = 0.0053


Model Results:


estimate       se     zval     pval    ci.lb    ci.ub

 -0.1126   0.0536  -2.0998   0.0357  -0.2177  -0.0075        *
```

g) Effects of covariates: left MOFC <- global SANS + length of illness + gender + age + site (if applicable)

Shown below are the estimate, the standard error, p value and the confidence intervals for the meta-analytical standardized regression beta of length of illness estimates on left MOFC thickness. Results were based on estimates from 13 studies.

```
Random-Effects Model (k = 13; tau^2 estimator: REML)


tau^2 (estimated amount of total heterogeneity): 0.0539 (SE =
0.0271)

tau (square root of estimated tau^2 value):      0.2321

I^2 (total heterogeneity / total variability):   86.66%

H^2 (total variability / sampling variability):  7.50
```

```
Test for Heterogeneity:
Q(df = 12) = 51.8783, p-val < .0001

Model Results:

estimate       se     zval     pval    ci.lb    ci.ub
 -0.0922   0.0719  -1.2836   0.1993  -0.2331   0.0486
```

h) Effects of covariates: left MOFC <- global SANS + length of illness + gender + age + site (if applicable)

Shown below are the estimate, the standard error, p value and the confidence intervals for the meta-analytical standardized regression beta of global SANS scores on left MOFC thickness. Results were based on estimates from 13 studies.

```
Random-Effects Model (k = 13; tau^2 estimator: REML)

tau^2 (estimated amount of total heterogeneity): 0.0079 (SE =
0.0069)
tau (square root of estimated tau^2 value):      0.0892
I^2 (total heterogeneity / total variability):   48.94%
H^2 (total variability / sampling variability):  1.96

Test for Heterogeneity:
Q(df = 12) = 22.8334, p-val = 0.0292

Model Results:

estimate       se     zval     pval    ci.lb    ci.ub
 -0.0681   0.0373  -1.8240   0.0682  -0.1413   0.0051        .
```

i) Moderation analysis of age of onset on the association between global SANS scores and left MOFC thickness

Shown below are the estimate, the standard error, p value and the confidence intervals for the moderating effects of age of onset on the meta-analytical standardized regression beta of global SANS scores on left MOFC thickness. Results were based on estimates from 13 studies.

Mixed-Effects Model (k = 13; tau^2 estimator: REML)

tau^2 (estimated amount of residual heterogeneity): 0.0077 (SE = 0.0072)

tau (square root of estimated tau^2 value): 0.0875

I^2 (residual heterogeneity / unaccounted variability): 46.82%

H^2 (unaccounted variability / sampling variability): 1.88

R^2 (amount of heterogeneity accounted for): 0.00%

Test for Residual Heterogeneity:

QE(df = 11) = 20.0562, p-val = 0.0446

Test of Moderators (coefficient(s) 2):

QM(df = 1) = 0.1133, p-val = 0.7365

Model Results:

	se	zval	pval	ci.lb	ci.ub	
intrcpt	-0.0651	0.0370	-1.7578	0.0788	-0.1377	0.0075 .
I(AO_mean - 23.83)	0.0050	0.0149	0.3365	0.7365	-0.0242	0.0342

j) Moderation analysis of antipsychotic medication on the association between global SANS scores and left MOFC thickness

To investigate potentially moderating effects of antipsychotic medication, we derived the percentages of patients treated with typical or atypical antipsychotics, both antipsychotic medication types and the percentage of unmedicated patients in each sample. Shown below are the estimate, the standard error, p value and the confidence intervals for the moderating effects of antipsychotic medication on the meta-analytical standardized regression beta of global SANS scores on left MOFC thickness. Percentages of participants on typical, atypical and combined antipsychotic medication were mean centered and compared to the percentage of unmedicated patients (baseline). The intercept refers to the effect of global SANS score on left MOFC thickness after accounting for antipsychotic medication. Results were based on estimates from 13 studies.

```
Mixed-Effects Model (k = 13; tau^2 estimator: REML)


tau^2 (estimated amount of residual heterogeneity):     0.0039 (SE =
0.0056)
tau (square root of estimated tau^2 value):             0.0621
I^2 (residual heterogeneity / unaccounted variability): 32.04%
H^2 (unaccounted variability / sampling variability):   1.47
```

```
R^2 (amount of heterogeneity accounted for):            0.00%

Test for Residual Heterogeneity:
QE(df = 9) = 11.9256, p-val = 0.2175

Test of Moderators (coefficient(s) 2,3,4):
QM(df = 3) = 2.6632, p-val = 0.4465

Model Results:

                      estimate      se     zval    pval    ci.lb   ci.ub
intrcpt                -0.0489  0.0318  -1.5375  0.1242  -0.1112  0.0134
I(MED_a_perc - 68.72)   0.0042  0.0031   1.3557  0.1752  -0.0019  0.0103
I(MED_b_perc - 8.536)   0.0009  0.0048   0.1812  0.8562  -0.0086  0.0103
I(MED_t_perc - 11.1)    0.0022  0.0038   0.5879  0.5566  -0.0052  0.0097
```

N.B.: predictor abbreviations refer to percentage of patients treated with atypical (MED_a_perc) or typical (MED_t_perc) antipsychotics, both antipsychotic medication types (MED_b_perc) and the percentage of unmedicated patients (intrcpt, i.e. baseline).

k) Moderation analysis of handedness on the association between global SANS scores and left MOFC thickness

To investigate potentially moderating effects of handedness, we derived the percentage of ambidextrous, left- and right-handed participants. Shown below are the estimate, the standard error, p value and the confidence intervals for the moderating effects of handedness on the meta-analytical standardized regression beta of global SANS scores on left MOFC thickness. Percentages of ambidextriuos and left-handed partipicants were mean centered and compared to the right-handed group (baseline). The intercept refers

to the effect of global SANS score on left MOFC thickness after accounting for handedness. Results were based on estimates from 14 studies.

```
Mixed-Effects Model (k = 14; tau^2 estimator: REML)


tau^2 (estimated amount of residual heterogeneity):     0.0061 (SE =
0.0059)

tau (square root of estimated tau^2 value):             0.0780

I^2 (residual heterogeneity / unaccounted variability): 44.65%

H^2 (unaccounted variability / sampling variability):   1.81

R^2 (amount of heterogeneity accounted for):            0.00%


Test for Residual Heterogeneity:

QE(df = 11) = 19.0779, p-val = 0.0597


Test of Moderators (coefficient(s) 2,3):

QM(df = 2) = 1.0884, p-val = 0.5803


Model Results:


                       estimate      se     zval    pval    ci.lb   ci.ub

intrcpt                 -0.0603  0.0342  -1.7634  0.0778  -0.1273  0.0067
.

I(HAND_a_perc - 3.591)   0.0010  0.0074   0.1399  0.8888  -0.0134  0.0154

I(HAND_l_perc - 8.688)  -0.0113  0.0116  -0.9744  0.3299  -0.0341  0.0115
```

N.B.: predictor abbreviations refer to the percentage of ambidextrous (HAND_a_perc), left-handed (HAND_l_perc) and right-handed patients (intrcpt, i.e. baseline).

l) Left MOFC thickness differences by antipsychotic medication type percentages

We also investigated whether left MOFC thickness differed by the percentage of patients treated with typical or atypical antipsychotics, both antipsychotic medication types and the percentage of unmedicated patients. Shown below are the estimate, the standard error, p value and the confidence intervals of mean left MOFC thickness for each antipsychotic medication group. Percentages were mean centered and compared to unmedicated patients (baseline). Results were based on estimates from 13 studies.

```
Mixed-Effects Model (k = 13; tau^2 estimator: REML)

tau^2 (estimated amount of residual heterogeneity):     0.0060 (SE = 0.0030)
tau (square root of estimated tau^2 value):             0.0777
I^2 (residual heterogeneity / unaccounted variability): 95.96%
H^2 (unaccounted variability / sampling variability):   24.73
R^2 (amount of heterogeneity accounted for):            44.87%

Test for Residual Heterogeneity:
QE(df = 9) = 249.4885, p-val < .0001

Test of Moderators (coefficient(s) 2,3,4):
QM(df = 3) = 12.2740, p-val = 0.0065

Model Results:

                      estimate        se     zval    pval    ci.lb   ci.ub
intrcpt                 2.4841  0.0222  111.8192  <.0001   2.4405   2.5276
***
I(MED_a_perc - 68.72)  -0.0058  0.0019   -3.1327  0.0017  -0.0094  -0.0022
**
I(MED_b_perc - 8.536)  -0.0026  0.0033   -0.7653  0.4441  -0.0091   0.0040
I(MED_t_perc - 11.1)   -0.0065  0.0022   -2.9253  0.0034  -0.0109  -0.0021
**
```

N.B.: predictor abbreviations refer to percentage of patients treated with atypical (MED_a_perc) or typical (MED_t_perc) antipsychotics, both antipsychotic medication types (MED_b_perc) and the percentage of unmedicated patients (intrcpt, i.e. baseline).

m) Global SANS score differences by antipsychotic medication type percentages

Furthermore, We also investigated whether global SANS scores differed by the percentage of patients treated with typical or atypical antipsychotics, both antipsychotic medication types and the percentage of unmedicated patients. Shown below are the estimate, the standard error, p value and the confidence intervals of mean global SANS scores for each antipsychotic medication group. Percentages were mean centered and compared to unmedicated patients (baseline). Results were based on estimates from 13 studies.

```
Mixed-Effects Model (k = 13; tau^2 estimator: REML)

tau^2 (estimated amount of residual heterogeneity):     7.3158 (SE = 3.5444)
tau (square root of estimated tau^2 value):             2.7048
I^2 (residual heterogeneity / unaccounted variability): 98.34%
H^2 (unaccounted variability / sampling variability):   60.25
R^2 (amount of heterogeneity accounted for):            0.00%

Test for Residual Heterogeneity:
QE(df = 9) = 483.0582, p-val < .0001

Test of Moderators (coefficient(s) 2,3,4):
QM(df = 3) = 2.6231, p-val = 0.4535

Model Results:
```

	estimate	se	zval	pval	ci.lb	ci.ub	
intrcpt	8.7936	0.7616	11.5460	<.0001	7.3009	10.2863	***
I(MED_a_perc - 68.72)	-0.0229	0.0627	-0.3648	0.7153	-0.1457	0.1000	
I(MED_b_perc - 8.536)	0.1342	0.1142	1.1748	0.2401	-0.0897	0.3581	
I(MED_t_perc - 11.1)	-0.0591	0.0758	-0.7793	0.4358	-0.2078	0.0895	

N.B.: predictor abbreviations refer to percentage of patients treated with atypical (MED_a_perc) or typical (MED_t_perc) antipsychotics, both antipsychotic medication types (MED_b_perc) and the percentage of unmedicated patients (intrcpt, i.e. baseline).

n) Left MOFC thickness differences by antipsychotic medication type percentages, covarying for gender and age

We also investigated whether left MOFC thickness differed by the percentage of patients treated with typical or atypical antipsychotics, both antipsychotic medication types and the percentage of unmedicated patients, when additionally controlling for gender and age. Shown below are the estimate, the standard error, p value and the confidence intervals of mean left MOFC thickness for each antipsychotic medication group. Percentages were mean centered and compared to unmedicated patients (baseline). Results were based on estimates from 13 studies.

```
Mixed-Effects Model (k = 13; tau^2 estimator: REML)

tau^2 (estimated amount of residual heterogeneity):     0.0076 (SE = 0.0043)
tau (square root of estimated tau^2 value):             0.0873
I^2 (residual heterogeneity / unaccounted variability): 96.44%
H^2 (unaccounted variability / sampling variability):   28.06
R^2 (amount of heterogeneity accounted for):            30.46%
```

```
Test for Residual Heterogeneity:
QE(df = 7) = 235.2282, p-val < .0001

Test of Moderators (coefficient(s) 2,3,4,5,6):
QM(df = 5) = 10.1896, p-val = 0.0700

Model Results:

                      estimate      se     zval    pval    ci.lb    ci.ub
intrcpt                 2.4799  0.0267  92.8312  <.0001   2.4276   2.5323
***
I(Age_mean - 34.72)    -0.0041  0.0100  -0.4115  0.6807  -0.0237   0.0155
I(MED_a_perc - 68.72)  -0.0056  0.0022  -2.5524  0.0107  -0.0098  -0.0013
*
I(MED_b_perc - 8.536)  -0.0016  0.0046  -0.3361  0.7368  -0.0106   0.0075
I(MED_t_perc - 11.1)   -0.0053  0.0035  -1.5391  0.1238  -0.0121   0.0015
I(MF_ratio - 2.255)    -0.0091  0.0386  -0.2365  0.8130  -0.0848   0.0666
```

N.B.: predictor abbreviations refer to percentage of patients treated with atypical (MED_a_perc) or typical (MED_t_perc) antipsychotics, both antipsychotic medication types (MED_b_perc) and the percentage of unmedicated patients (intrcpt, i.e. baseline) as well as the ratio of males versus females (MF_ratio).

o) Left MOFC thickness differences by antipsychotic medication type percentages, covarying for gender and length of illness

We also investigated whether left MOFC thickness differed by the percentage of patients treated with typical or atypical antipsychotics, both antipsychotic medication types and the percentage of unmedicated patients, when additionally controlling for gender and length of ilness. Shown below are the estimate, the standard error, p value

and the confidence intervals of mean left MOFC thickness for each antipsychotic medication group. Percentages were mean centered and compared to unmedicated patients (baseline). Results were based on estimates from 11 studies.

```
Mixed-Effects Model (k = 11; tau^2 estimator: REML)

tau^2 (estimated amount of residual heterogeneity):     0.0087 (SE = 0.0057)
tau (square root of estimated tau^2 value):             0.0932
I^2 (residual heterogeneity / unaccounted variability): 97.07%
H^2 (unaccounted variability / sampling variability):   34.16
R^2 (amount of heterogeneity accounted for):            31.69%

Test for Residual Heterogeneity:
QE(df = 5) = 187.9049, p-val < .0001

Test of Moderators (coefficient(s) 2,3,4,5,6):
QM(df = 5) = 9.6171, p-val = 0.0868

Model Results:

                      estimate      se     zval    pval    ci.lb    ci.ub
intrcpt                 2.4693  0.0348  70.9461  <.0001   2.4011   2.5376
***
I(LOI_mean - 10.74)    -0.0077  0.0119  -0.6514  0.5148  -0.0310   0.0155
I(MED_a_perc - 68.72)  -0.0051  0.0025  -2.0599  0.0394  -0.0100  -0.0002
*
I(MED_b_perc - 8.536)   0.0013  0.0074   0.1793  0.8577  -0.0132   0.0159
I(MED_t_perc - 11.1)   -0.0042  0.0036  -1.1451  0.2522  -0.0113   0.0030
I(MF_ratio - 2.255)     0.0089  0.0644   0.1384  0.8899  -0.1172   0.1350
```

N.B.: predictor abbreviations refer to percentage of patients treated with atypical (MED_a_perc) or typical (MED_t_perc) antipsychotics, both antipsychotic medication types (MED_b_perc) and the

percentage of unmedicated patients (intrcpt, i.e. baseline) as well as the ratio of males versus females (MF_ratio) and mean length of illness (LOI_mean).

p) Moderation analysis of single vs multisite status on the association between global SANS scores and left MOFC thickness

Shown below are the estimate, the standard error, p value and the confidence intervals for the moderating effects of single vs multisite status on the meta-analytical standardized regression beta of global SANS scores on left MOFC thickness. The intercept refers to the effect of global SANS score on left MOFC thickness after accounting for single vs multisite status. Results were based on estimates from 17 studies.

```
Mixed-Effects Model (k = 17; tau^2 estimator: REML)

tau^2 (estimated amount of residual heterogeneity):     0.0078 (SE =
0.0066)
tau (square root of estimated tau^2 value):             0.0886
I^2 (residual heterogeneity / unaccounted variability): 45.43%
H^2 (unaccounted variability / sampling variability):   1.83
R^2 (amount of heterogeneity accounted for):            0.00%

Test for Residual Heterogeneity:
QE(df = 15) = 25.9669, p-val = 0.0384

Test of Moderators (coefficient(s) 2):
QM(df = 1) = 0.6443, p-val = 0.4222

Model Results:
```

	estimate	se	zval	pval	ci.lb	ci.ub
intrcpt	-0.0954	0.0409	-2.3295	0.0198	-0.1756	-0.0151
*						
as.factor(multisite)1	0.0567	0.0706	0.8027	0.4222	-0.0817	0.1950

q) Effects of covariates: left MOFC <- global SANS + CPZ + gender + age + site (if applicable)

Shown below are the estimate, the standard error, p value and the confidence intervals for the meta-analytical standardized regression beta of current chlorpromazine equivalents (CPZ, based on Woods *et al*. (2003)) on left MOFC thickness. Results were based on estimates from 12 studies.

```
Random-Effects Model (k = 12; tau^2 estimator: REML)

tau^2 (estimated amount of total heterogeneity): 0.0003 (SE =
0.0040)
tau (square root of estimated tau^2 value):      0.0160
I^2 (total heterogeneity / total variability):   2.26%
H^2 (total variability / sampling variability):  1.02

Test for Heterogeneity:
Q(df = 11) = 9.7194, p-val = 0.5558

Model Results:

estimate       se     zval     pval    ci.lb    ci.ub
 -0.0413   0.0301  -1.3717   0.1701  -0.1003   0.0177
```

r) Effects of covariates: left MOFC <- global SANS + CPZ + gender + age + site (if applicable)

Shown below are the estimate, the standard error, p value and the confidence intervals for the meta-analytical standardized regression beta of global SANS scores on left MOFC thickness, controlling for current chlorpromazine equivalents (based on Woods *et al*. (2003)). Results were based on estimates from 12 studies.

```
Random-Effects Model (k = 12; tau^2 estimator: REML)

tau^2 (estimated amount of total heterogeneity): 0.0120 (SE =
0.0104)
tau (square root of estimated tau^2 value):      0.1093
I^2 (total heterogeneity / total variability):   52.08%
H^2 (total variability / sampling variability):  2.09

Test for Heterogeneity:
Q(df = 11) = 22.4039, p-val = 0.0214

Model Results:

estimate       se     zval     pval    ci.lb    ci.ub
 -0.0950   0.0462  -2.0564   0.0397  -0.1856  -0.0045        *
```

s) Effects in DSM-IV schizophrenia subtypes or schizoaffective / -phreniform disorder only: left MOFC <- global SANS + CPZ + gender + age + site (if applicable)

Schizophrenia inclusion criteria were site-specific. In detail, five sites included only patients with DSM-IV subtypes of schizophrenia. Eight sites also included schizoaffective and schizophreniform

patients in their samples, while only a minority of sites (N_{sites}=4; 7% of our total sample) also included a few patients with other psychotic disorders, such as psychotic disorder NOS.

Of those sites where individual diagnostic codes for patients were available to us (N_{sites}=11, including the four sites with patients with other psychotic disorders), 77% of patients were diagnosed with Schizophrenia subtypes and 12% with schizoaffective / -phreniform disorders.

To ensure that our results were not influenced by including patients with other psychotic disorders, we repeated the analyses including only patients with DSM-IV schizophrenia subtypes or schizoaffective / -phreniform disorders.

Shown below are the estimate, the standard error, p value and the confidence intervals for the meta-analytical standardized regression beta of global SANS scores on left MOFC thickness, including only patients with DSM-IV schizophrenia subtypes or schizoaffective / -phreniform disorders. Results were based on estimates from 16 studies.

```
Random-Effects Model (k = 16; tau^2 estimator: REML)

tau^2 (estimated amount of total heterogeneity): 0.0060 (SE = 0.0061)
tau (square root of estimated tau^2 value):      0.0774
I^2 (total heterogeneity / total variability):   36.24%
H^2 (total variability / sampling variability):  1.57

Test for Heterogeneity:
Q(df = 15) = 22.6004, p-val = 0.0930
```

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	
-0.0780	0.0339	-2.2992	0.0215	-0.1445	-0.0115	*

SM 2.2 Exploratory analyses on ten more frontal regions

Univariate models were used to analyse the effect of negative symptoms on ten other frontal regions (separately for the left and right hemisphere; see SM Table 3s), controlling for sex, age and site (if applicable). After Bonferroni correction for multiple testing (ten regions per hemisphere = 20 tests), two regions remained significant on the left hemisphere, while no effect was observed in any of the regions on the right side (SM Table 3s).

	left hemisphere		*right hemisphere*		
region-of-interest	βstd	*p*	βstd	*p*	Nsites
caudalmiddlefrontal	-0.0196	0.5052	-0.0474	0.1406	17
lateralorbitofrontal	-0.0756	0.0017	-0.0732	0.0114	17
caudalanteriorcingulate	-0.0164	0.5169	-0.0547	0.0921	13
parsopercularis	-0.0821	0.001	-0.0357	0.2544	15
parsorbitalis	-0.0512	0.0512	-0.0479	0.0897	13
parstriangularis	-0.0659	0.0101	-0.0422	0.086	15
rostralanteriorcingulate	0.0137	0.6022	-0.0434	0.1884	13
rostralmiddlefrontal	-0.0509	0.0446	-0.0484	0.0613	17

superiorfrontal	-0.0662	0.0223	-0.0640	0.0264	17
frontalpole	-0.0398	0.1149	0.0006	0.9821	13

SM Table 3s. Exploratory analyses on ten more frontal regions.

References

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